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Review

Effects of bisphenol A and its analogs on reproductive health: A mini review

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ABSTRACT

Known endocrine disruptor bisphenol A (BPA) has been shown to be a reproductive toxicant in animal models. Its structural analogs: bisphenol S (BPS), bisphenol F (BPF), bisphenol AF (BPAF), and tetrabromobisphenol A (TBBPA) are increasingly being used in consumer products. However, these analogs may exert similar adverse effects on the reproductive system, and their toxicological data are still limited. This mini-review examined studies on both BPA and BPA analog exposure and reproductive toxicity. It outlines the current state of knowledge on human exposure, toxicokinetics, endocrine activities, and reproductive toxicities of BPA and its analogs. BPA analogs showed similar endocrine potencies when compared to BPA, and emerging data suggest they may pose threats as reproductive hazards in animal models. While evidence based on epidemiological studies is still weak, we have utilized current studies to highlight knowledge gaps and research needs for future risk assessments.

1. Introduction

Bisphenol A (BPA) is a high production volume (HPV) chemical, commonly used in food packaging materials, dental sealants, medical devices and thermal receipts [1]. Exposure to BPA is ubiquitous *via* ingestion, inhalation, and dermal contact [2,3]. The Centers for Disease Control and Prevention (CDC) has reported measurable levels of BPA in urine samples in over 90% of the United States population [4,5]. BPA has demonstrated endocrine disrupting effects by interacting with various physiological receptors, such as estrogen receptor α/β (ER α/β), estrogen-related receptor γ, androgen receptor (AR), and thyroid hormone receptor [6–13]. Numerous studies have investigated the reproductive toxicity of BPA, and extensive reviews were conducted to address the strength of the evidence regarding BPA toxicity [14]. In 2006, an expert panel composed of the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Dental Craniofacial Research (NIDCR), the U.S. Environmental Protection Agency (EPA), and Commonweal, reviewed human exposure to BPA *in vivo* and *in vitro* [15]. The subpanel of experts that focused on *in vivo* animal studies found contradictory results among the studies. However, they were confident that BPA impacted the male and female reproductive system [14]. Peretz et al. summarized studies published from 2007 to 2013 to examine the associations between BPA and adverse reproductive outcomes [14]. Based on the evidence from experimental animals and human exposure from 2007 to 2013, the authors concluded that BPA at doses below the LOAEL (50 mg/kg/day) impacted female reproduction and had potential adverse effects on the male reproductive system [14]. Furthermore, recent epidemiological studies have indicated that BPA exposure may potentially be associated with alterations in hormone levels, impairment of ovary and uterine function, and reduction of sperm quality [16–20]. Current data from experimental studies have suggested that BPA exposure adversely affected oocyte quality and maturation, decreased sperm production and quality, damaged testicular cells, perturbed hormone levels, and disrupted ovary function and uterine morphology in animal models [21–28].

Due to widespread exposure and concerns that BPA is a reproductive toxicant, the public drove manufacturers to abandon the use of BPA and introduce analogous chemicals in baby bottles, sippy cups, and infant formula packaging [29,30]. The U.S. Food and Drug Administration then ruled that BPA would no longer be used in the products mentioned above [29,30]. BPA analogs are being used as cross-linking reagents and flame retardants in the plastics industry to produce "BPA-free" products. However, the usage of these chemicals is expected

Abbreviations: 3β-HSD, 3β-hydroxysteroid dehydrogenase; AR, androgen receptor; BPA, bisphenol A; BPAF, bisphenol AF; BPF, bisphenol F; BPS, bisphenol S; CDC, the US Centers for Disease Control and Prevention; E2, estradiol; EC20, 20% maximal effect concentration; ER α/β, estrogen receptor α/β; ER, endoplasmic reticulum; EPA, the United States Environmental Protection Agency; FDA, the U.S. Food and Drug Administration; FSH, follicle-stimulating hormone; GD, gestational day; HTS, high throughput screening; LH, luteinizing hormone; LOAEL, the lowest adverse effect level; NHANES, the National Health and Nutrition Examination Survey; NTP, the National Toxicology Program; P4, progesterone; PF, post-fertilization; PND, postnatal day; ROS, reactive oxygen species; T, testosterone; T3, triiodothyronine; T4, thyroxine; TBBPA, tetrabromobisphenol A; TSH, thyroid-stimulating hormone

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Table 1
BPA and oocyte outcomes in experimental studies.

Source	Animal	Strain	Exposure route	Time of exposure	Doses	Age at collection	Summary	Reference
Moore-Ambriz et al., 2015	Mouse	C57BL/6J	Oral dose[a]	3 estrous cycle	50 μg/kg	After the 3 estrous cycles	Young (PND 28–32) female rats were exposed to BPA at a dose of 50 μg/kg during the first estrous cycle. In *in vivo* and *in vitro* fertilization assay, BPA exposure significantly decreased the percentage of fertilized oocytes. No changes of ovulation were observed	[25]
Ferris et al., 2015	Bovine		*In vitro* oocyte	24 h	15 and 30 ng/mL		In bovine oocyte, exposure to 30 ng/mL BPA (130 nM) decreased meiosis progression and increased spindle abnormalities, including abnormal spindle morphology and chromosome alignment	[44]
Wang et al., 2016b	Porcine		*In vitro* oocyte		250 μM		BPA exposure (250 μM) increased ROS abnormal cytoskeletons, apoptosis/autophagy rate and altered epigenetic pattern in porcine oocytes	[28]
Ferris et al., 2016	Bovine		*In vitro* cumulus oocyte complexes	8 days	65 and 130 nM		Bovine oocytes exposed to BPA were fertilized in embryo culture and showed significant DNA damage and apoptosis at 130 nM, while gene expression in blastocysts was not altered.	[24]
Nakano et al., 2016	Mouse	ICR	*In vitro* oocyte	6, 9, 12, 15 and 18 h	2, 20, 50 and 100 μg/mL		BPA exposure inhibited oocyte maturation at concentrations of 50 and 100 μg/mL and delayed the cell cycle at a dose of 2 μg/mL. Further BPA treatment caused spindle abnormalities and activated the spindle assembly checkpoint at a dose of 50 μg/mL	[45]

[a] Placing a pipette tip with the dosing solution in the corner of the animal mouth.

to rise globally despite a lack of production data for these analogs. Recently, the prevalence of BPA analogs in the environment, foods, consumer products, and human urine samples have been reported [31–35]. With high degrees of structural similarities to BPA, these analogs may potentially have a similar endocrine disrupting capacity and the potential to exert adverse effects on the reproductive system. Emerging evidence suggests that BPA analogs interact with various physiological receptors, such as estrogen receptors α and β, androgenic receptors, and aryl hydrocarbon receptors [36,37]. Compared to BPA, little is known about the reproductive toxicity of these analogs. Here, we have reviewed the current literature on BPA, its analogs, and male/female reproduction to summarize the current state of knowledge and the gaps in that knowledge, and to highlight future research directions that could provide valuable information for toxicity evaluation and risk assessment. In addition, the environmental occurrences, human biomonitoring data, toxicokinetics, and the endocrine disrupting capacity of BPA analogs have also been included. This review is structured into 7 topics: (1) BPA and female reproductive health; (2) BPA and male reproductive health; (3) BPS and reproductive health; (4) BPF and reproductive health; (5) BPAF and reproductive health; (6) TBBPA and reproductive health; (7) conclusion and research needs. This review of recent literature focuses on the effects of BPA and its analogs on the male and female reproductive system. We hope the information and conclusions in this review could direct future studies and be useful in risk assessment and in the formation of regulations regarding BPA and its analogs.

2. Search strategy

We performed a literature search to identify journal articles related to BPA, BPS, BPF, BPAF, and TBBPA exposure and reproduction. The research included articles published between 2014 and 2017 for BPA and all years up to 2017 for BPA analogs. An electronic search was performed in Pubmed (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.com/). Pubmed was selected to identify journal articles as it is considered a main and reliable literature source. Google Scholar was used as a much broader search engine to collect and analyze any literature that may not have been included in Pubmed. Search terms included:

{'Bisphenol A' OR 'BPA' OR 'bisphenol S' OR 'BPS' OR '4,4′-sulfonyldiphenol' OR 'bisphenol F' OR 'BPF' OR '4,4′-dihydroxydiphenylmethane' OR 'bisphenol AF' OR 'BPAF' OR 'hexafluorobisphenol A' OR 'tetrabromobisphenol A' OR 'TBBPA' OR '2,2′,6,6′-Tetrabromo-4,4′-isopropylidenediphenol'} AND {'reproductive' OR 'oocyte' OR 'ovary' OR 'uterus' OR 'testes' OR 'sperm' OR 'Leydig cell' OR 'Sertoli cell' OR 'steroidogenesis' OR 'estradiol' OR 'testosterone' OR 'follicle-stimulating hormone' OR 'luteinizing hormone' OR 'thyroid' OR 'pregnenolone'}.

3. BPA and female reproductive health

3.1. Oocyte production and quality

Experimental studies conducted prior to 2014 provided compelling evidence that BPA had the potential to affect two stages of oogenesis. The onset of meiosis in fetal ovaries, germ cell nest breakdown, and follicle formation were concluded to be the main causes of BPA adversely affecting maturing oocytes. Three studies found that gestational exposure to low-dose BPA in mice induced increased expression of *Stra8* and a variety of meiotic genes in C57BL/6 mice [38], where longer gestational exposure down-regulated the expression of *Stra8, Dazl,* and *Nobox* in CD-1 mice [39]. These results suggested that BPA exposure can cause alterations of gene expression in germ cells and early meiocytes. In neonatally exposed lambs, low-dose BPA was reported to increase the number of multi-oocyte follicles [40], where another study using macaques with low-dose dietary BPA exposure also showed